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Reference:
Anttila Verneri, Bulik-Sullivan Brendan, Finucane Hilary K., Walters Raymond K., Bras Jose, Duncan Laramie, Escott-Price Valentina, Falcone Guido J., Gormley Padhraig, Malik Rainer, ...- Analysis of shared heritability in common disorders of the brain
Science / American Association for the Advancement of Science [Washington, D.C.] - ISSN 0036-8075 - 360:6395(2018), eaap8757
Full text (Publisher's DOI): https://doi.org/10.1126/SCIENCE.AAP8757
To cite this reference: http://hdl.handle.net/10067/1519630151162165141

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Title: Analysis of Shared Heritability in Common Disorders of the Brain

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One Sentence Summary: Comprehensive heritability analysis of brain phenotypes demonstrates a clear role for common genetic variation across neurological and psychiatric disorders and behavioral-cognitive traits, with substantial overlaps in genetic risk.

Abstract: Disorders of the brain can exhibit considerable epidemiological comorbidity and share symptoms, provoking debate about their etiologic overlap. We quantified the genetic sharing of 25 brain disorders from genome-wide association studies of 215,683 patients and 657,164 controls, and their relationship to 17 phenotypes from 1,191,588 individuals. Psychiatric disorders share common variant risk, while neurological disorders appear more distinct from one another and from the psychiatric disorders. We also identify significant sharing between disorders and a number of brain phenotypes, including cognitive measures. Simulations were used to explore how power, diagnostic misclassification and phenotypic heterogeneity affect genetic correlations. These results highlight the importance of common genetic

variation as a risk factor for brain disorders and the value of heritability-based methods in understanding their etiology.

Main Text:

The classification of brain disorders has evolved over the past century, reflecting the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, spontaneous movements or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders(*1*). Understanding the genetic underpinnings and categorical distinctions between brain disorders may be helpful in informing the search for the biological pathways underlying their pathophysiology(*2, 3*).

In general, brain disorders (excepting those caused by trauma, infection, or cancer) show substantial heritability from twin and family studies(*4*). Epidemiological and twin studies have explored patterns of phenotypic overlaps(*5-7*), and comorbidity has been reported for many pairs of disorders, including bipolar disorder-migraine(*8*), stroke-major depressive disorder(MDD)(*9*), epilepsy-autism spectrum disorders (ASD), and epilepsy-attention deficit hyperactivity disorder (ADHD)(*10, 11*). Furthermore, there may also be direct etiological links, as e.g. mutations in the same ion channel genes confer pleiotropic risk for multiple distinct brain phenotypes(*12-14*). Genome-wide association studies (GWAS) have demonstrated that individual common risk variants can overlap across traditional diagnostic boundaries(*15, 16*), and that disorders like schizophrenia, MDD, and bipolar disorder can have genetic correlations(*17*).

GWAS have also demonstrated that common genetic variation contributes to the heritability of brain disorders. Generally, this occurs via the combination of many common variants, each with a small individual effect, with examples in Alzheimer's disease(*18*), bipolar disorder(*19*), migraine(*20*), Parkinson's disease(*21*), and schizophrenia(*22*). In addition to locus discovery, the degree of distinctiveness(*23*) across neurological and psychiatric phenotypes can be evaluated with the introduction of novel heritability-based methods(*24*) and sufficiently large sample sizes for robust heritability analysis. These analyses can shed light on the nature of these diagnostic boundaries and explore the extent of shared common variant genetic influences.

Study design

The Brainstorm consortium is a collaboration among GWAS meta-analysis consortia of 25 disorders (see Table 1), to perform a comprehensive heritability and correlation analysis of brain disorders. We included meta-analyses of any common brain disorders for which we could identify a GWAS meta-analysis consortium of sufficient size for heritability analysis. The total study sample consists of 215,683 cases of different brain disorders and 657,164 controls (Table 1), and

includes at least one representative of most ICD-10 blocks covering mental and behavioral disorders and diseases of the central nervous system. Also included are 1,191,588 samples for 13 "behavioral-cognitive" phenotypes (n=744,486) traditionally viewed as brain-related, and four "additional" phenotypes (n=447,102) selected to represent known, well-delineated etiological processes (immune disorders [Crohn's disease], vascular disease [coronary artery disease] and anthropomorphic measures [height and BMI]; Table 2).

GWAS summary statistics for the 42 disorders and phenotypes were centralized and underwent uniform quality control and processing(*25*)*(83)*. We used European-only meta-analyses for each disorder to avoid potential bias arising from ancestry differences, generating new meta-analyses for those datasets where the original sample sets had diverse ancestries. Clinically relevant subtypes from three disorders (epilepsy, migraine, and ischemic stroke) were also included; in these cases, the subtype datasets are parts of the top-level dataset (Table 1).

We have developed a heritability estimation method, linkage disequilibrium score regression (LDSC)(*24*), which was used to calculate heritability estimates and correlations, as well as to estimate their statistical significance from block jack-knife-based standard errors. More formally, we estimate the common variant heritability (h^2g) of each disorder, defined as the proportion of phenotypic variance in the population that could theoretically be explained by an optimal linear predictor formed using the additive effects of all common (minor allele frequency > 5%) autosomal SNPs. The genetic correlation for a pair of phenotypes is then defined as the correlation between their optimal genetic predictors. Heritability for binary disorders and phenotypes was transformed to the liability scale. We further performed a weighted-least squares regression analysis to evaluate whether differences relating to study makeup (such as sample size) were correlated with the magnitude of the correlation estimates. Finally, we performed a heritability partitioning analysis*(83)* using stratified LD score regression to examine whether the observed heritability for the disorders or phenotypes was enriched into any of the tissue-specific regulatory regions or functional category partitions of the genome, using ten top-level tissue-type and 53 functional partitions from Finucane et al.(*26*). Finally, simulated phenotype data was generated under different scenarios by permuting 120,267 genotyped individuals from the UK Biobank(*25*) to evaluate power and aid in interpreting the results(*83*).

Heritability estimates and their error sources

We observed a similar range of heritability estimates among the disorders and the behavioral-cognitive phenotypes (Fig. S1A-B and Table S1, S2), roughly in line with previously reported estimates from smaller datasets (Table S3). Three ischemic stroke subtypes (cardioembolic, large-vessel disease, and small-vessel disease) as well as the "agreeableness" personality measure from NEO Five-Factor Inventory(*27*) had insufficient evidence of additive heritability for robust analysis and thus were excluded from further analysis(*25*). The only

observed correlation between heritability estimates and factors relating to study makeup (Table S4; Fig. S1C-F) was a modest correlation between age of onset of the disorder and heritability, suggesting that early-onset brain disorders tend to be more heritable. Since some of our interpretation of the results depends on lack of observed correlation, we explored the behavior of observed correlation versus power (Fig. S2A), standard errors (Fig. S2B) and the individual results (Fig. S2C and D) to identify where we can be reasonably robust in claiming lack of correlation.

The common variant heritability estimates for the psychiatric and neurological disorders were generally somewhat lower than previously reported estimates from common variants (Table S5). A similar pattern was observed for the behavioral-cognitive traits, when comparing estimates reported here with those previously reported in smaller sample sizes(*28*) with the exception of 'openness', 'neuroticism', and 'never/ever smoked', suggesting that some attenuation in heritability is observed when moving to larger sample sizes. Measures related to cognitive ability, such as childhood cognitive performance (heritability estimate of 0.19, [SE 0.03]) and years of education (heritability estimate of 0.30 [SE 0.01]), yielded estimates that were more consistent with previous estimates of the heritability of intelligence(*29, 30*), suggesting that the cognitive measures may be less prone to phenotypic measurement error and/or have a higher heritability overall than the personality measures.

These heritability estimates should be interpreted somewhat cautiously, as they reflect the phenotype ascertained in each study, and will be deflated in the presence of diagnostic heterogeneity, ascertainment errors or unusual contributions of high-impact rare variants. To evaluate potential sources of these differences, we explored three approaches*(83)*: evaluating the differences in real data, simulation work (Table S5), and quantifying the magnitude of effect for potentially implied misclassification (Table S6).

In comparison to heritability estimates obtained using twin and family data, the more diverse selection and survival biases in the underlying data may attenuate the heritability estimates and correlations, as might increased within-disorder heterogeneity introduced by the larger meta-analyses. A related explanation for the lower estimates of heritability may be that increasing sample sizes have led to expanded inclusion criteria, meaning that less severely affected cases with a lower overall burden of risk factors (both genetic and environmental) might be included, which in turn would attenuate estimates of heritability. However, the successful identification of genome-wide significant loci suggests that these larger samples are nevertheless very useful for genetic studies, and the simulation results suggest that this has at most a limited effect on estimated genetic correlations (Fig S9). Even so, some of the pairs of phenotypes included here lack sufficient power for robust estimation of genetic correlations. Moreover, our analyses only examine the properties of common variant contributions and extending these analyses to include the effects of rare variants may further inform the extent of genetic overlap. For example, epilepsy and ASD show substantial overlap in genetic risk from de novo loss of functional mutations(*31*), in contrast to the limited common variant sharing observed in this study. This may suggest that the rare and common

variant contributions to genetic overlap may behave differently and that incorporating the two variant classes into a single analysis may provide further insight into brain disorder pathogenesis.

To address the possibility of methodological differences contributing to the differences in the estimates and although LDSC and REML have previously been shown to yield similar estimates from the same data(*24*), we performed our own comparison in Alzheimer's disease(*32*) (selected based on data availability). In Alzheimer's disease, the previously published heritability estimate (0.24 [SE 0.03]) is significantly different from the estimate in the current study (0.13 [SE 0.02]). These differences may reflect implicit heterogeneity in a much larger case collection used in the current study (effective sample size 10,494 vs. 46,669) and the potential reasons listed above, but they could also be due to methodological variability (most of the previous estimated listed in Table S3 are estimated with a different methodology). To evaluate this, we applied the same analytical process used in this paper to the summary statistics of the GERAD cohort (3,941 cases and 7,848 controls) from the Alzheimer's disease meta-analysis, where the previous heritability estimate was calculated. There, we obtained a heritability estimate of 0.25 [SE 0.04], which agrees closely with the published estimate of 0.24 [SE 0.03], suggesting that the different estimates may reflect differences between datasets rather than methodological variability.

Correlations among brain disorders

We observed widespread sharing across psychiatric disorders (Fig. 1 and S3) by expanding the number of brain disorder pairs studied beyond those previously reported(*17*), but similar sharing was not observed among neurological disorders. Among the psychiatric disorders, schizophrenia showed significant genetic correlation with most of the psychiatric disorders, while MDD was positively (though not necessarily significantly) correlated with every other disorder tested. Further, schizophrenia, bipolar disorder, anxiety disorders, MDD, and ADHD each showed a high degree of correlation to the four others (average genetic correlation [r_g]=0.40; Table S7A). Anorexia nervosa, obsessive-compulsive disorder (OCD), and schizophrenia also demonstrated significant sharing amongst themselves (Fig. 1). However, the common variant risk of both ASD and Tourette Syndrome (TS) appear to be distinct from other psychiatric disorders, although with significant correlation between TS, OCD, and MDD, as well as between ASD and schizophrenia. Similarly, post-traumatic stress disorder (PTSD) showed no significant correlation with any of the other psychiatric phenotypes (though some correlation to ADHD and MDD was observed). The modest power of the ASD, PTSD, and TS meta-analyses, however, limits the strength of this conclusion (Fig. S2C).

Neurological disorders showed a more limited extent of genetic correlation than the psychiatric disorders (Fig. 2 and S4, Table S7A), suggesting greater diagnostic specificity and/or more distinct etiologies. Parkinson's disease, Alzheimer's disease, generalized epilepsy, and multiple sclerosis showed little to no correlation with other brain disorders. The highest degree of

genetic correlation among the neurological disorders was observed with focal epilepsy (average r_g =0.46, excluding the other epilepsy datasets), though none were significant, reflecting the relatively modest power of the current focal epilepsy meta-analysis (Fig. S2C). However, the modest heritability and the broad pattern of sharing observed for focal epilepsy may be consistent with heterogeneity and potentially even diagnostic misclassification across a range of neurological conditions.

In the cross-category correlation analysis, the observed pattern is consistent with limited sharing across the included neurological and psychiatric disorders (Fig. 3; average r_g=0.03). The only significant cross-category correlations were with migraine, suggesting it may share some of its genetic architecture with psychiatric disorders; migraine-ADHD (r_g=0.26, p=8.81 x 10^{-8}), migraine-TS (r_g=0.19, p=1.80 x 10^{-5}), and migraine-MDD (r_g=0.32, p=1.42 x 10^{-22} for all migraine, r_g=0.23, p=5.23 x 10^{-5} for migraine without aura, r_g=0.28, p=1.00 x 10^{-4} for migraine with aura).

We observed several significant genetic correlations between the behavioral-cognitive or additional phenotypes and brain disorders (Fig. 4 and Table S7B). Results for cognitive traits were dichotomous among psychiatric phenotypes (Fig. S5A), with ADHD, anxiety disorders, MDD, and TS showing negative correlations to the cognitive measures and anorexia nervosa, ASD, bipolar disorder and OCD showing positive correlations. Schizophrenia showed more mixed results, with significantly negative correlation to intelligence but positive correlation to years of education. Among neurological phenotypes (Fig. S5B), the correlations were either negative or null, with Alzheimer's disease, epilepsy, ICH, ischemic stroke, early-onset stroke, and migraine showing significantly negative correlations. Correlations between college attainment and years of education with bipolar disorder(*24*), Alzheimer's disease, and schizophrenia have been previously reported(*33*)).

Among the personality and symptom measures, significant positive correlations were observed between neuroticism and anorexia nervosa, anxiety disorders, migraine, migraine without aura, MDD, OCD, schizophrenia, and TS (Fig. S6A and S6B; replicating previously reported correlations with MDD and schizophrenia(34)); between depressive symptoms and ADHD, anxiety disorder, bipolar disorder, MDD, and schizophrenia; and between subjective well-being and anxiety disorder, bipolar disorder, and MDD. For smoking-related measures, the only significant genetic correlations were between never/ever smoked and MDD (r_g=0.33, p=3.10 x 10^{-11}) as well as ADHD (r_g=0.37, p=3.15 x 10^{-6}).

Among the additional phenotypes, the two examples of disorders with well-defined etiologies had different results. Crohn's disease, representing immunological pathophysiology, showed no correlation with any of the study phenotypes, while the phenotype representing vascular pathophysiology (coronary artery disease) showed significant correlation to MDD (r_g=0.19, p=8.71 x 10^{-5}) as well as the two stroke-related phenotypes (r_g=0.69, p=2.47 x 10^{-6} to ischemic stroke and r_g=0.86, p=2.26 x 10^{-5} to early-onset stroke), suggesting shared genetic effects across

these phenotypes. Significant correlations were also observed for BMI, which was positively correlated with ADHD and MDD, and negatively correlated with anorexia nervosa (as previously reported with a different dataset(*24*)) and schizophrenia.

Our enrichment analysis (Fig. S7, Tables S8-12) demonstrated significant heritability enrichments between central nervous system (CNS) and generalized epilepsy, MDD, TS, college attainment, intelligence, neuroticism, never/ever smoked); depressive symptoms and adrenal/pancreatic cells and tissues, as well as between hematopoetic cells (category which includes immune system cells) and multiple sclerosis (Figs. S7A and S7B, Tables S8 and S9). We replicate the reported (CNS) enrichment for schizophrenia, bipolar disorder, and years of education (Tables S8, S9), and observe the reported enrichments for BMI (CNS), years of education (CNS), height (connective tissues and bone, cardiovascular system and other), and Crohn's disease (hematopoietic cells) from the same datasets (Fig. S7C, D)(*26*). We further note that the psychiatric disorders with large numbers of identified GWAS loci (bipolar disorder, MDD, and schizophrenia) and migraine, which was the only cross-correlated neurological disorder, show enrichment to conserved regions (Tables S10 and S12), while the other neurological disorders with similar numbers of loci (MS, Alzheimer's, and Parkinson's diseases) do not (Fig. S7A, B). Enrichment to conserved regions was also observed to neuroticism, intelligence and college attainment and to H3K9ac peaks for BMI (Tables S11 and S12).

Discussion

By integrating and analyzing the genome-wide association summary statistic data from consortia of 25 brain disorders, we find that psychiatric disorders broadly share a considerable portion of their common variant genetic risk, especially across schizophrenia, MDD, bipolar disorder, anxiety disorder, and ADHD, while neurological disorders are more genetically distinct. Across categories, psychiatric and neurologic disorders share relatively little common genetic risk, suggesting that multiple different and largely independently regulated etiological pathways may give rise to similar clinical manifestations (e.g., psychosis, which manifests in both schizophrenia(*35*) and Alzheimer's disease(*36*)). Except for migraine, which appears to share some genetic architecture with psychiatric disorders, the existing clinical delineation between neurology and psychiatry is corroborated at the level of common variant risk for the studied disorders.

We performed some exploratory analyses based on the observed results to address concerns about diagnostic overlap and misclassification, which are particularly relevant to psychiatric disorders due to their spectral nature. Given that the broad and continuous nature of psychiatric disorder spectra has long been clinically recognized(*37-39*) and that patients can, in small numbers, progress from one diagnosis to another(*40*), we evaluated to what extent this kind of diagnostic overlap could explain the observed correlations. Genetic correlation could arise if, for example,

patients progress through multiple diagnoses over their lifetime, or if some specific diagnostic boundaries between phenotype pairs are particularly porous to misclassification (Table S5). While it would *a priori* appear unlikely to observe large-scale misclassification of migraine as schizophrenia, for example, there may be more substantial misclassification between particular psychiatric disorders, consistent with the clinical controversies in classification. Previous work(*41*) suggests that substantial misclassification (on the order of 15-30%, depending on whether it is uni- or bi-directional) is required to introduce false levels of genetic correlation. We found that the observed levels of correlation are unlikely to appear in the absence of underlying genetic correlation (Table S6), as it is apparent that a very high degree of misclassification (up to 79%) would be required to produce the observed correlations in the absence of any true genetic correlation, and that reasonably expected misclassification would have limited impact on the observed r_g (Fig. S8). Therefore, these results suggest true sharing of a substantial fraction of the common variant genetic architecture among psychiatric disorders as well as between behavioral-cognitive measures and brain disorders. We also performed large-scale simulations to explore the effect of sample size, polygenicity and degree of correlation on power to detect significant correlations. First, we established that the observed heritability of the simulated misclassified traits in the UK Biobank data behaves as would be theoretically expected (Fig. S9A), and that the effects on observed correlation (Fig. S9B and S9C) are in line with the estimates from family data(*41*). Reasonably low levels of misclassification or changes to the exact level of heritability appear unlikely to induce significant correlations, as observed in the power analysis (Fig. S10), though a lower observed heritability caused by substantial misclassification (Fig. S9A) will decrease the power to estimate true genetic overlap.

The high degree of genetic correlation among the psychiatric disorders adds further evidence that current clinical diagnostics do not reflect specific genetic etiology for these disorders, and that genetic risk factors for psychiatric disorders do not respect clinical diagnostic boundaries. Rather, this suggests a more interconnected genetic etiology, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. This study may provide important 'scaffolding' to support a framework for investigating mental disorders, incorporating many levels of information to understand basic dimensions of brain function.

The observed positive genetic correlations are consistent with a few hypothetical scenarios. For example, it may reflect the existence of some portion of common genetic risk factors conferring risks for multiple psychiatric disorders and where other distinct additional factors, both genetic and non-genetic, contribute to the eventual clinical presentation. The presence of significant genetic correlation may also reflect the phenotypic overlap between any two disorders; for example, the sharing between schizophrenia and ADHD might reflect underlying difficulties in executive functioning, which are well-established in both disorders(*42*), and that the shared risk arises from a partial capture of its shared genetic component. Similarly, we might speculate that a shared mechanism underlying cognitive biases may extend from overvalued ideas to delusions (ranging from anorexia nervosa and OCD to schizophrenia), and that this heritable intermediate

trait confers pleiotropic risk to multiple outcomes. This kind of latent variable could give rise to the observed genetic correlation between disorders due to the shared portion of variation affecting that variable. While a combination of these is likely, more genome-wide significant loci are needed to evaluate these overlaps at the locus level.

Conversely, the low correlations observed across neurological disorders suggest that the current classification reflects relatively specific genetic etiologies, although the limited sample size for some of these disorders and lack of inclusion of disorders conceived as "circuit-based" in the literature, such as restless legs syndrome, sleep disorders and possibly essential tremor, constrains the full generalizability of this conclusion. Degenerative disorders (such as Alzheimer's and Parkinson's diseases) would not be expected *a priori* to share their polygenic risk profiles with a neuro-immunological disorder (like multiple sclerosis) or neurovascular disorder (like ischemic stroke). Similarly, we see limited evidence for the reported co-morbidity between migraine with aura and ischemic stroke(*43*) (r_g=0.29, p=0.099); however, the standard errors of this comparison are too high to draw strong conclusions. At the disorder subtype level, migraine with and without aura (r_g=0.48, p=1.79 x 10^{-5}) shows substantial genetic correlation, while focal and generalized epilepsy (r_g=0.16, p=0.388) show much less.

The few significant correlations across neurology and psychiatry, namely between migraine and ADHD, MDD, and TS, suggest modest shared etiological overlap across the neurology/psychiatry distinction. The co-morbidity of migraine with MDD, TS and ADHD has been previously reported in epidemiological studies(*44-47*), while in contrast, the previously reported co-morbidity between migraine and bipolar disorder seen in epidemiological studies (*48*) was not reflected in our estimate of genetic correlation (r_g=-0.03, p=0.406).

Several phenotypes show only very low-level correlations with any of the other disorders and phenotypes studied here, despite large sample size and robust evidence for heritability, suggesting their common variant genetic risk may largely be unique. Alzheimer's disease, Parkinson's disease, and multiple sclerosis show extremely limited sharing with the other phenotypes and with each other. Neuroinflammation has been implicated in the pathophysiology of each of these conditions(*49-51*), as it has for migraine(*52*) and many psychiatric conditions, including schizophrenia(*53*), but no considerable shared heritability was observed with either of those conditions nor with Crohn's disease, nor did we observe enrichment for immune-related tissues in the functional partitioning (Fig. S7) as for Crohn's disease. While this does not preclude the sharing of individual neuroinflammatory mechanisms in these disorders, the large-scale lack of shared common variant genetic influences supports the distinctiveness of disorder etiology. Further, we only observed significant enrichment of heritability for immunological cells and tissues in multiple sclerosis, showing that inflammation-specific regulatory marks in the genome do not show overall enrichment for common variant risk for either Alzheimer's or Parkinson's diseases (though this does not preclude the effects of specific, non-polygenic neuroinflammatory mechanisms(*54*)). Among psychiatric disorders, ASD and TS showed a similar absence of correlation with other disorders, although this could reflect small sample sizes.

Analysis of the Big Five personality measures suggest that the current sample sizes may be large enough for correlation testing; neuroticism, which has by far the largest sample size, shows several significant correlations. Most significant of these was to MDD (r_g=0.737, p=5.04 x 10^{-96}), providing evidence for the link between these phenotypes, as reported for polygenic risk scores(*55*) and twin studies(*56, 57*); as well as other psychiatric disorders (Fig. 4, Table S7B). The correlation between MDD and anxiety disorders, with a similar pattern of correlation and the dimensional measures of depressive symptoms, subjective well-being, and neuroticism suggests that they all tag a similar underlying etiology. The significant correlation between coronary artery disease and MDD supports the link between MDD and CAD(*58*), while the observed correlation between ADHD and smoking initiation (r_g=0.374, p=3.15 x 10^{-6}) is consistent with the epidemiological evidence of overlap(*59*) and findings from twin studies(*60*).

For the neurological disorders, five (Alzheimer's disease, intracerebral hemorrhage, ischemic and early-onset stroke, and migraine) showed significant negative genetic correlation to the cognitive measures, while a two (epilepsy and focal epilepsy) showed moderate negative genetic correlation (Fig. S5). For Alzheimer's disease, poor cognitive performance in early life has been linked to increased risk for developing the disorder(*61*), but to our knowledge no such connection has been reported for other phenotypes. Among the psychiatric disorders, ADHD, anxiety disorders and MDD show a significant negative correlation to cognitive and education attainment measures, while the remaining five of the eight psychiatric disorders (anorexia nervosa, ASD, bipolar disorder, OCD, and schizophrenia) showed significant positive genetic correlation with one or more cognitive measures. These results suggest the existence of a link between cognitive performance in early life and the genetic risk for both psychiatric and neurological brain disorders. The basis of the genetic correlations between education, cognition and brain disorders may have a variety of root causes including indexing performance differences on the basis of behavioral dysregulation (e.g., ADHD relating to attentional problems during cognitive tests) or may reflect ascertainment biases in certain disorders conditional on impaired cognition (e.g., individuals with lower cognitive reserve being more rapidly identified for Alzheimer's disease), but the results could also suggest a direct link between the underlying etiologies.

BMI shows significant positive genetic correlation to ADHD, consistent with a meta-analysis linking ADHD to obesity(*62*), and negative genetic correlation with anorexia nervosa, OCD, and schizophrenia. This is consistent with evidence for enrichment of BMI heritability in CNS tissues(*26*) that suggest neuronal involvement(*63*); this may also provide a partial genetic explanation for lower BMI in anorexia nervosa patients even after recovery(*64*). Given that no strong correlations were observed between BMI and any of the neurological phenotypes, it may be that BMI's brain-specific genetic architecture is more closely related to behavioral phenotypes. Ischemic stroke and BMI show surprisingly little genetic correlation in this analysis (r_g=0.07, p=0.26), suggesting that although BMI is a risk factor for stroke(*65*), there is little evidence for shared common genetic effects. These analyses also suggest that the reported reduced rates of cardiovascular disease in individuals with histories of anorexia nervosa(*66, 67*) are more likely

due to BMI-related secondary effects. The limited evidence of genetic correlation of anorexia nervosa with intracerebral hemorrhage, ischemic stroke, early-onset stroke and coronary artery disease suggest that any lower cardiovascular mortality is more likely due to direct BMI-related effects rather than genetic risk variants.

The genetic correlation results presented here indicate that the clinical boundaries for the studied psychiatric phenotypes do not reflect distinct underlying pathogenic processes. This suggests that genetically informed analyses may provide a basis for restructuring of psychiatric nosology, consistent with twin and family-based results. In contrast, neurological disorders show greater genetic specificity, and although it is important to emphasize that while some brain disorders are under-represented here, our results demonstrate the limited evidence for widespread common genetic risk sharing between psychiatric and neurological disorders. However, we provide strong evidence that both psychiatric and neurological disorders show robust correlations with cognitive and personality measures, suggesting new avenues for follow-up studies. Further study is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments give hope to reducing diagnostic heterogeneity and eventually improving the diagnostics and treatment of psychiatric disorders.

Materials and Methods

We collected GWAS meta-analysis summary statistics for 25 brain disorders and 17 other phenotypes from various consortia, and where necessary generated new, non-sex-stratified European-cohorts-only versions of the meta-analyses(*25*). All datasets underwent uniform quality control *(83).* For each trait, using the linkage disequilibrium score (LDSC) framework(*24*), the total additive common SNP heritability present in the summary statistics (h^2g) was estimated by regressing the association χ^2 statistic of a SNP against the total amount of common genetic variation tagged by that SNP, for all SNPs. Genetic correlations (r_g; i.e., the genome-wide average shared genetic risk) for pairs of phenotypes were estimated by regressing the product of Z-score for each phenotype and for each SNP, instead of the χ^2 statistic. Significance was assessed by Bonferroni multiple testing correction via estimating the number of independent brain disorder phenotypes via matrix decomposition *(83)*. Functional and partitioning analyses for the GWAS datasets were also performed using LDSC. Power analyses and simulation work to aid in interpretation of the results were conducted using genotype data from the UK Biobank Resource *(83)*.

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Acknowledgments We thank the members of the Neale and Daly labs for helpful discussions, and to acknowledge R. Hoskins, J. Wessman and J. Martin for their comments on the manuscript, M. Whittall for inspiration, S. Knemeyer for help with the summary figure, C. Hammond for organizational assistance, and the patients and participants of the respective consortia for their invaluable participation. Data on coronary artery disease has been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG. matSpD is available at neurogenetics.qimrberghofer.edu.au/matSpD/. This research has been conducted using the UK Biobank Resource (application #18597). **Funding:** This work was supported by grants 1R01MH10764901 and 5U01MH09443203 as well as the Orion Farmos Research Foundation (VA) and the Fannie and John Hertz Foundation (HKF); disorder-specific funding is detailed in the Supplementary Materials ("Study-specific acknowledgments"). **Author contributions:** VA, AC and BMN conceived and coordinated the study; VA, BBS, HKF, RW and PT contributed methodology; BBS and HKF contributed software; VA and BMN conducted the statistical analysis; BMN obtained funding and provided resources; RW, JB, LD, VE-P, GF, PG, RM, NP, SR, ZW, and DY were responsible for curation of disorder-specific data; PHL and CC helped with data interpretation; VA and BMN wrote the original draft, and all authors contributed to review and editing; VA provided the visualization; GB, CB, MDaly, MDichgans, SVF, RG, PH, KK, BK, CAM, AP, JS, PS, JW, NW, CC, AP, JS, PS, JR, AC, BMN provided supervision and project administration; remaining authors contributed disorder-specific sample collection and/or analysis (Consortium-specific lists can be found in the Supplementary Materials). **Competing interests:** Authors report no competing interests. **Data and materials availability:** Data sources for the GWAS summary statistics used in the study and their availability, as well as the study-specific acknowledgments, are listed in Supplementary Materials (Table S13 and Supplementary text, respectively).

Figure 1. *Genetic correlations across psychiatric phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder.

Figure 2. *Genetic correlations across neurological phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. Some phenotypes have substantial overlaps (see Table 1), e.g. all cases of generalized epilepsy are also cases of epilepsy. Asterisks indicate significant genetic correlation after multiple testing correction. ICH – intracerebral hemorrhage.

Figure 3. *Genetic correlations across neurological and psychiatric phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder.

Figure 4. *Genetic correlations across brain disorders and behavioral-cognitive phenotypes.*

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance (LDSC), with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significantly different from zero after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; PTSD – post-traumatic stress disorder; BMI –body-mass index.

Table 1. *Brain disorder phenotypes used in the Brainstorm project.*

Psychiatric disorders				**Neurological disorders**			
Disorder	Source	Cases	Controls	Disorder	Source	Cases	Controls
ADHD	PGC-ADD2	12,645	84,435	Alzheimer's disease	IGAP	17,008	37,154
Anorexia nervosa	PGC-ED	3,495	11,105	Epilepsy	ILAE	7,779	20,439
Anxiety disorders	ANGST	5,761	11,765	Focal epilepsy	"	4,601	17,985
Autism spectrum disorder	PGC-AUT	6,197	7,377	Generalized epilepsy	"	2,525	16,244
Bipolar disorder	PGC-BIP2	20,352	31,358	Intracerebral hemorrhage	ISGC	1,545	1,481
Major depressive disorder	PGC-MDD2	16,823	25,632	Ischemic stroke	METASTROKE	10,307	19,326
OCD	PGC-OCDTS	2,936	7,279	Cardioembolic stroke	"	1,859	17,708
PTSD	PGC-PTSD	2,424	7,113	Early-onset stroke	"	3,274	11,012
Schizophrenia	PGC-SCZ2	33,640	43,456	Large-vessel disease	"	1,817	17,708
Tourette Syndrome	PGC-OCDTS	4,220	8,994	Small-vessel disease	"	1,349	17,708
				Migraine	IHGC	59,673	316,078
				Migraine with aura	"	6,332	142,817
				Migraine without aura	"	8,348	136,758
				Multiple sclerosis	IMSGC	5,545	12,153
				Parkinson's disease	IPDGC	5,333	12,019
Total psychiatric		*108,493*	*238,514*	*Total neurologic*		*107,190*	*418,650*

Indented phenotypes are part of a larger whole, e.g. the epilepsy study contains the samples from both focal epilepsy and generalized epilepsy; sample counts for such overlaps are shown in gray. ADHD – attention deficit hyperactivity disorder; OCD – obsessive-compulsive disorder. 'Anxiety disorders' refers to a meta-analysis of five subtypes (generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and specific phobias). References are listed in Table S1 and data availability in Table S13.

Table 2. *Behavioral-cognitive and additional phenotypes used in the study.*

Phenotype	Source	Samples
Behavioral-cognitive phenotypes		
Cognitive		
Years of education (q)	SSGAC	293,723
College attainment (d)	"	120,917
Cognitive performance (q)	"	17,989
Intelligence (d)	CTG	78,308
Personality measures		
Subjective well-being	SSGAC	298,420
Depressive symptoms	"	161,460
Neuroticism (q)	"	170,911
Extraversion (q)	GPC	63,030
Agreeableness (q)	"	17,375
Conscientiousness (q)	"	17,375
Openness (q)	"	17,375
Smoking-related		
Never/ever smoked (d)	TAG	74,035
Cigarettes per day (q)	TAG	38,617
Additional phenotypes		
BMI (q)	GIANT	339,224
Height (q)	"	253,288
Coronary artery disease (d)	Cardiogram	86,995
Crohn's disease (d)	IIBDGC	20,883
Total		**1,124,048**

Indented phenotypes are part of a larger whole, e.g. samples in the college attainment analysis are a subset of those in the analysis for years of education; sample counts for such overlaps are shown in gray. (d) – dichotomous phenotype, (q) – quantitative phenotype. BMI – body-mass index. References and phenotype definitions are listed in Table S2, and data availability in Table S13.

Supplementary Materials

Materials and methods

Supplementary Text

Effect of co-morbidity and phenotypic misclassification

Study-specific acknowledgements

Consortium memberships

Figures S1-10

Tables S1-13

Print summary for aap8757, *Analysis of Shared Heritability in Common Disorders of the Brain,* by Anttila V. et al.

Introduction

Disorders of the brain can exhibit considerable epidemiological comorbidity and share symptoms, provoking debate about their etiologic overlap. However, detailed study of phenotypes with different ages of onset, severity and presentation presents a considerable challenge. Recently developed heritability methods allow us to accurately measure correlation of genome-wide common variant risk between two phenotypes from pools of different individuals, to understand how connected they, or at least their genetic risks, are on the genomic level. We quantified the degree of overlap for genetic risk factors of 25 common brain disorders, based on genome-wide association data for 215,683 patients and 657,164 controls, as well as 17 phenotypes from a total of 1,191,588 individuals.

Rationale

The classification of brain disorders has evolved over the last century, reflecting the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders. Understanding the genetic underpinnings and categorical distinctions for brain disorders and related phenotypes may inform the search for their biological mechanisms.

Results

Common variant risk for psychiatric disorders was shown to correlate significantly, especially between ADHD, bipolar disorder, major depressive disorder (MDD) and schizophrenia. In contrast, neurological disorders appear more distinct from one another and from the psychiatric disorders, except for migraine, which was significantly correlated to ADHD, MDD and Tourette Syndrome. We demonstrate that the personality trait neuroticism in the general population is significantly correlated with almost every psychiatric disorder and migraine. We also identify significant sharing between disorders and early life cognitive measures in the general population (e.g. years of education and college attainment), demonstrating positive correlation with several psychiatric disorders (e.g. anorexia nervosa and bipolar disorder) and negative correlation with several neurological phenotypes (e.g. Alzheimer's disease and ischemic stroke), even though the latter are considered to result from specific processes that occur later in life. Extensive simulations were also performed to inform how power, diagnostic misclassification and phenotypic heterogeneity influence genetic correlations.

Conclusion

The high degree of genetic correlation among many of the psychiatric disorders adds further evidence that the current clinical boundaries among them do not reflect distinct underlying pathogenic processes, at least on the genetic level. This suggests a deeply interconnected nature, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. Genetically informed analyses may provide important 'scaffolding' to support such restructuring of psychiatric nosology, which likely requires incorporating many levels of information. In contrast, we find limited evidence for widespread common genetic risk sharing among neurological disorders or across neurological and psychiatric disorders. We show that both psychiatric and neurological disorders have robust correlations with cognitive and personality measures. Further study is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments give hope to reducing heterogeneity and eventually improving the diagnosis and treatment of psychiatric disorders.

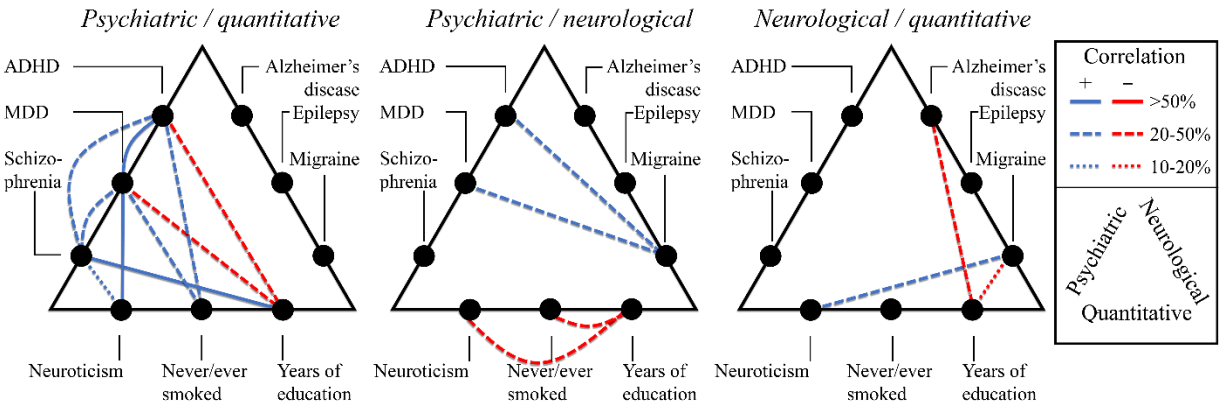

Figure Caption

Subsection of genetic risk correlations among brain disorders and quantitative phenotypes.

Heritability analysis of brain disorders points to pervasive sharing of genetic risk among psychiatric disorders, largely absent among neurological disorders, but present from both groups to neuro-cognitive quantitative phenotypes. Only significant correlations shown. Color and line solidity indicate direction and magnitude of correlation, respectively. ADHD – attention deficit hyperactivity disorder; MDD – major depressive disorder.

ADHD
Anorexia nervosa
Anxiety disorders
ASD
Bipolar disorder
MDD
OCD
PTSD
Schizophrenia
Tourette Syndrome

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
$<3.35 \times 10^{-4}$

Alzheimer's disease
Epilepsy
Focal epilepsy
Generalized epilepsy
ICH
Ischemic stroke
Early-onset stroke
Migraine
Migraine with aura
Migraine without aura
Multiple sclerosis
Parkinson's disease

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
<3.35 x 10^{-4}

Alzheimer's disease
Epilepsy
Focal epilepsy
Generalized epilepsy
ICH
Ischemic stroke
Early-onset stroke
Migraine
Migraine with aura
Migraine without aura
Multiple sclerosis
Parkinson's disease

ADHD
Anorexia nervosa
Anxiety disorders
ASD
Bipolar disorder
MDD
OCD
PTSD
Schizophrenia
Tourette Syndrome

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
* <3.35 x 10^{-4}

ADHD
Anorexia nervosa
Anxiety disorders
ASD
Bipolar disorder
MDD
OCD
PTSD
Schizophrenia
Tourette Syndrome
Alzheimer's disease
Epilepsy
Focal epilepsy
Generalized epilepsy
ICH
Ischemic stroke
Early-onset stroke
Migraine
Migraine with aura
Migraine without aura
Multiple sclerosis

College attainment
Years of education
Cognitive performance
Intelligence

Neuroticism
Extraversion
Conscientiousness
Openness
Depressive symptoms
Subjective well-being

Never/ever smoked
Cigarettes per day

BMI
Height
Crohn's disease
Myocardial infarction

Genetic correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

P-value significance
0.8
0.6
0.4
0.2
0.05
0.001
* <2.30 x 10^{-4}